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Primer

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Cytokine storm

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Abstract

Cytokine storm describes a spectrum of clinical manifestations that feature increased cytokine levels in circulation owing to overactivated immune responses. These increased concentrations of cytokines can cause tissue and organ damage, potentially leading to lethality. Cytokine storm can be induced by a variety of underlying clinical conditions, including infection, auto-inflammatory and autoimmune conditions, monogenic causes, or therapeutic intervention, which often makes diagnosis and treatment difficult. However, studies have identified conserved molecular mechanisms that inform therapeutic strategies. Cytokine storm is initiated by cytokine production and exacerbated by a self-amplifying positive feedback loop between cytokines and inflammatory cell death (PANoptosis). The process begins when cells detect triggers and undergo inflammatory signalling to produce and release cytokines via canonical secretion pathways or through lytic cell death such as pyroptosis and PANoptosis. This release of inflammatory cytokines, and potentially of other damage-associated molecules, can then drive inflammation and cell death in neighbouring cells through paracrine PANoptosis, resulting in further cytokine release and the amplification of the cycle. Improved understanding of the molecular and cellular mechanisms driving cytokine storm is critical for developing effective therapeutic strategies and improving clinical outcomes.

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Introduction

Cytokine storm refers to a spectrum of clinical manifestations resulting from overactivated immune responses, characterized by increased cytokine release that can lead to severe and often life-threatening tissue damage and organ damage[1–3] (Box 1). Cytokine storm was originally described in 1993 as a severe adverse reaction to allogenic bone marrow transplantation[4], and the clinical presentation closely resembled macrophage activation syndrome (MAS) — a phenomenon that was observed for the first time in the same year[5]. Since its first description, cytokine storm has been observed in response to a range of conditions, including genetic disorders (for example, familial (that is, primary) haemophagocytic lymphohistiocytosis (HLH) and perforin pathway-related diseases), infectious diseases (such as sepsis or influenza- or COVID-19-associated pneumonitis), and rheumatological or autoimmune conditions (for example, systemic lupus erythematosus (SLE), Kawasaki disease and inflammatory bowel disease)[3,6]. Additionally, malignancies (such as lymphoma) and immune-modulating therapies, including chimeric antigen receptor (CAR) T cell therapy, can also trigger cytokine storm[3,6,7]. Although cytokine storm is occasionally referred to as MAS, secondary HLH, cytokine storm syndrome or cytokine release syndrome (CRS), the unifying pathophysiological and clinical characteristics of these syndromes highlight that cytokine storm represents a common mechanistic pathway that occurs downstream of a diverse set of physiological causes[1,3].

Several studies have identified the molecular mechanisms driving cytokine storm, in which cytokine production, inflammatory signalling, immune dysfunction and cell death pathways interact in a self-amplifying feedback loop[1,2]. Specifically, pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), cytokines and other homeostatic disruptions activate innate immune sensors[8], which drive cytokine production through NF-κB, p38, JNK, AP-1 and interferon signalling pathways. These cytokines are then released through canonical secretory pathways or through lytic cell death. Upon release, cytokines activate cytokine receptors and innate immune sensors on neighbouring cells to drive cell death (paracrine PANoptosis) or other inflammatory signalling pathways, releasing more cytokines in the local tissue environment and into the bloodstream. This cascade culminates in a systemic cytokine storm — resulting in tissue and organ damage that can be widespread, severe and difficult to manage given the systemic effects throughout the body's critical systems[1,3] (Fig. 1).

In this Primer, we discuss the molecular and clinical features of cytokine storm, including its epidemiology, pathophysiology, clinical management and therapeutics. Given the severe clinical burden of cytokine storm across diverse conditions, understanding the underlying mechanisms in depth will inform the development of more targeted therapies to mitigate inflammation and improve patient outcomes.

Epidemiology

The exact incidence of cytokine storm is not well defined. Epidemiological studies of cytokine storm are challenging, as a diverse range of conditions can serve as underlying triggers leading to monogenic cytokine storm and non-monogenic forms such as pathogen-induced, autoimmune and auto-inflammatory, or therapeutic intervention-induced cytokine storm. Each individual subtype of cytokine storm is rare; however, in aggregate, these disorders are not uncommon. Additionally, genetic predisposition can increase the chances of an individual developing cytokine storm.

Box 1 | Terms and definitions

Cytokine storm
A pathological state of markedly elevated circulating cytokine levels, leading to systemic inflammation, vascular leakage, tissue injury and multiorgan dysfunction.

Cytokine release syndrome
A clinically defined syndrome caused by cytokine storm; the term is most commonly used in therapeutic intervention-induced cytokine storm, such as in response to CAR T cell therapy, but can also be used in other conditions, such as haemophagocytic lymphohistiocytosis, macrophage activation syndrome, systemic juvenile idiopathic arthritis and sepsis.

Haemophagocytic lymphohistiocytosis
A pathology caused by defective cytotoxic T lymphocyte function, leading to sustained T cell and macrophage activation, hypercytokinaemia, haemophagocytosis and multiorgan failure. Familial (genetic) or secondary (associated with infection, malignancy or autoimmunity) forms exist.

Macrophage activation syndrome
A rheumatological subtype of secondary haemophagocytic lymphohistiocytosis, most commonly associated with systemic juvenile idiopathic arthritis. It features macrophage overactivation, cytopenias, coagulopathy and markedly elevated levels of ferritin and liver enzymes in the serum.

Multi-system inflammatory syndrome in children
A post-infectious hyperinflammatory disorder following SARS-CoV-2 infection, marked by fever, cardiovascular shock, mucocutaneous inflammation and elevated cytokines; resembles Kawasaki disease or toxic shock syndrome.

PANoptosis
An innate immune, lytic cell death pathway initiated by innate immune sensors and driven by caspases and receptor-interacting protein kinases. PANoptosis results from innate immune cells detecting pathogen-associated molecular patterns, damage-associated molecular patterns and homeostatic disruptions, which can lead to cytokine release. Following the initial cytokine release, these cytokines can engage innate immune receptors on neighbouring cells to induce paracrine PANoptosis and perpetuate cytokine release.

Sepsis
A life-threatening organ dysfunction caused by a dysregulated host response to infection. Early in sepsis, the immune system often exhibits a hyperinflammatory phase, characterized by elevated circulating cytokines, endothelial activation and widespread tissue inflammation.

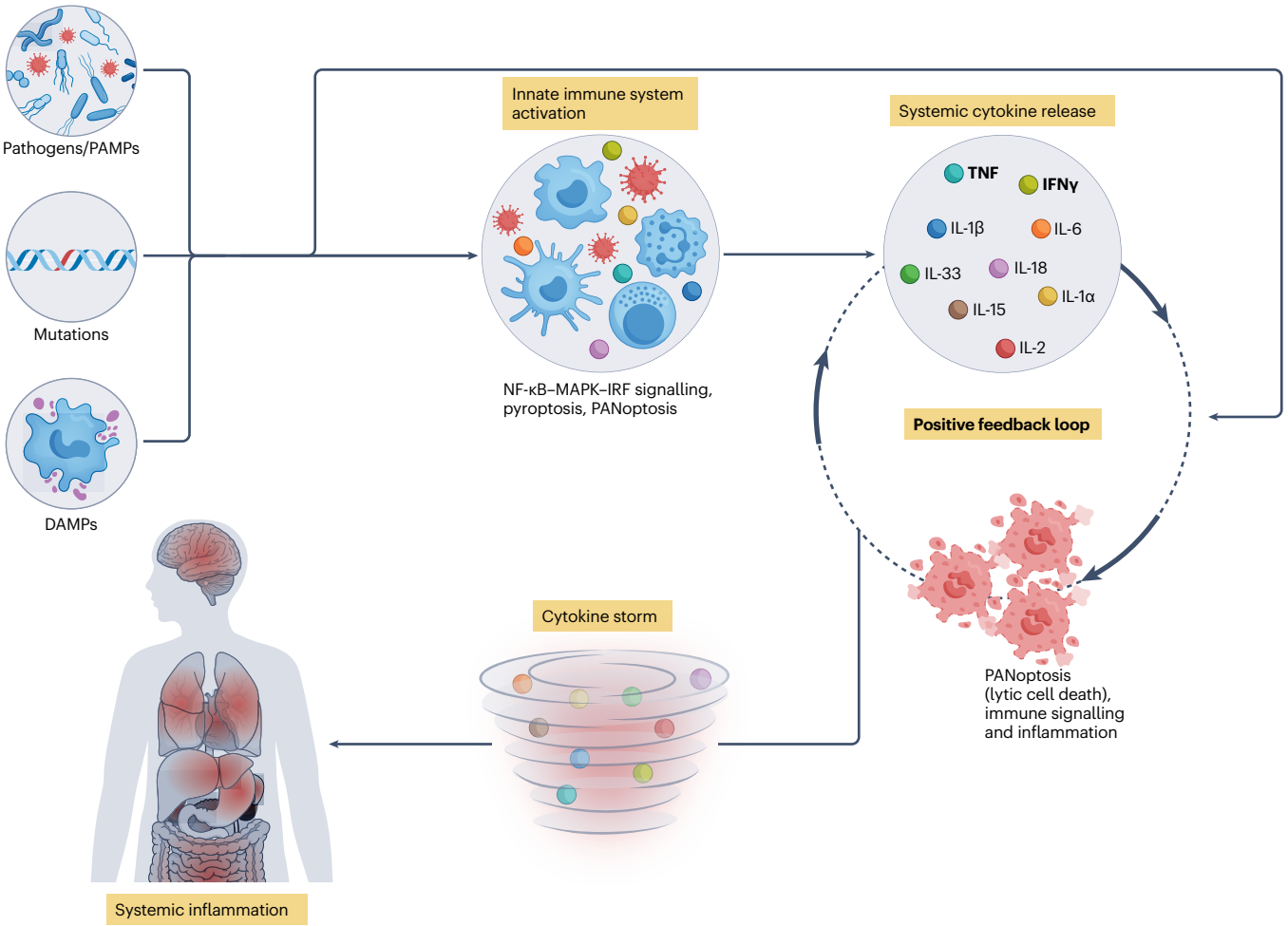

Fig. 1 | Schematic representation of cytokine storm initiation and amplification. In response to genetic mutations leading to autoimmune and auto-inflammatory diseases, infections, inflammatory conditions, and other cytokine storm-inducing conditions, immune cells become activated and release various pro-inflammatory cytokines as well as damage-associated molecular patterns (DAMPs). The synergism of TNF and IFNγ, and potentially other cytokines, can trigger PANoptosis, further amplifying cytokine production. Certain pathogens, such as viruses (for example, SARS and MERS) and bacteria (for example, *Francisella*), and pathogen-associated molecular patterns (PAMPs) can also directly induce cytokine production and inflammatory cell death via PANoptosis. This positive feedback loop of inflammatory cytokine production and cell death can ultimately lead to cytokine storm, with potential tissue and organ damage and mortality.

Monogenic cytokine storm

Although genetic disorders that directly cause cytokine storm are rare, they do occur. The prototypical example is primary HLH, where patients have mutations in genes that control immune activation of cytotoxic T lymphocytes and natural killer cells (for example, *PRF1*, *UNC13D*, *STX11* and *STXBP2*), leading to sustained T cell and macrophage activation that causes cytokine release and damage throughout the body[9]. The frequency of primary HLH varies based on ethnicity and geographic region. A study of primary HLH in Texas estimated a prevalence of 1 per 100,000 children[10], whereas another study has reported an incidence of 1.2 per 1,000,000 children in Sweden[11].

Genetic defects can also drive cytokine storm in the context of mutations that disrupt other aspects of immune homeostasis regulation. For example, mutations that cause excess inflammasome activation, which drive the release of the inflammatory cytokines IL-1β and IL-18, also cause cytokine storm. Specific mutations in *NLRP3* cause cryopyrin-associated periodic syndromes that have an incidence ranging from 1 to 3 per million individuals, based on a study in France (with an estimated prevalence of 1 in 360,000)[12], and mutations in *MEFV* in familial Mediterranean fever syndromes have an incidence ranging from 1 per 500–1,000 individuals in Armenia and Turkey[13,14] to 1 in 465,500 throughout central Europe[15]. NLRC4 is another inflammasome activator but the incidence of mutations in *NLRC4* that are observed in certain MAS and multi-system inflammatory conditions is largely unknown owing to its rarity. Furthermore, retrospective epidemiological studies likely underestimate the incidence and prevalence of genetically driven cytokine storm due to misclassification of such conditions as sepsis or sudden unexplained deaths in infancy when autopsies and genetic testing are not performed. Additionally, frequencies are likely to be underestimated in low-resource settings, where the availability of genetic testing and immunological studies is limited[11,16].

Non-monogenic cytokine storm

Studies have reported several non-monogenic forms of cytokine storm. For epidemiological purposes, the clinical condition called secondary HLH — the pathophysiology of which resembles HLH but occurs in the absence of a mutation known to drive primary HLH — can be considered as a surrogate for these non-genetic forms of cytokine storm. Infectious, inflammatory or malignant conditions and their treatment can precipitate secondary HLH. A study from the UK using national electronic health records to estimate secondary HLH noted that the incidence quadrupled between 2003 and 2018, with a reported incidence of ~1–4 per 1,000,000 individuals in 2018 (ref. 17). There was no increase in incidence in patients <5 years of age (the population most likely to have primary HLH), and researchers found that the increase in HLH incidence in older patients most likely reflects improved identification of the condition owing to increased clinical recognition[17]. This analysis preceded the COVID-19 pandemic, which further raised awareness of cytokine storm syndromes. Cytokine storm was mentioned infrequently in the literature prior to the SARS-CoV-2 outbreak, with citations increasing dramatically during the pandemic[18]. Additionally, many disorders that can be causative of secondary HLH, such as inflammatory bowel disease, have been increasing in frequency[19]. Collectively, this suggests that the latest increases in the incidence of cytokine storm syndromes likely reflect a combination of a true rise in incidence and an increase in awareness of the condition.

Pathogen-induced cytokine storm. The epidemiology of pathogen-induced cytokine storm, including sepsis-related and SARS-CoV-2-related cytokine storm, is particularly difficult to estimate owing to the variability in infectious triggers and clinical definitions of cytokine storm. Many infections that are associated with cytokine storm have seasonal and geographic variability[20]. Furthermore, infections that may be causative, such as dengue, are endemic to specific regions while being infrequent in North America and Europe, making the incidence and prevalence of the subsequent cytokine storm highly regionally variable[21]. For example, Epstein–Barr virus-triggered cytokine storm is a classic example of an infection-triggered cytokine storm; however, its prevalence varies based on geographical region, with higher rates of cytokine storm, such as chronic active Epstein–Barr virus, in Asia and South America than in the USA[22]. Cytokine storm secondary to SARS-CoV-2 was a substantial concern during the COVID-19 pandemic, and a retrospective cohort study found the incidence of secondary HLH in patients with COVID-19 in the intensive care unit to be 8.7%[23].

Sepsis is another well-known pathogen-driven condition that is commonly associated with cytokine storm. Although the incidence of sepsis itself is known to be ~677.5 per 100,000 globally[24], the prevalence of cytokine storm among these cases is not well documented. In general, overall estimates of the incidence and prevalence of cytokine storm that results from infection remain challenging to determine.

Autoimmune-induced or auto-inflammation-induced cytokine storm. In addition to infections, another well-characterized aetiology of cytokine storm is autoimmune or auto-inflammatory disease. MAS is a term used to specifically denote cytokine storm or HLH secondary to autoimmune diseases. MAS is estimated to complicate ~10% of cases of systemic juvenile idiopathic arthritis (sJIA), with as many as 30–40% of these patients having subclinical features of MAS[25–27]. Similarly, MAS has been reported in 10% of patients with childhood onset of SLE, and studies have reported MAS as a complication of almost all rheumatological diseases[27,28].

Malignancy-induced cytokine storm. Malignancy-associated cytokine storm is the most common form in adult patients, although it is rare in paediatric patients[29,30]. Approximately 40–60% of cytokine storm cases or secondary HLH cases in adults are due to malignancy[30]. The incidence of malignancy-associated cytokine storm or HLH from 2012 to 2018 was estimated to be ~0.45 per 100,000 adults. Malignancy-associated cytokine storm or HLH can occur with any type of cancer but it is most commonly observed in patients with lymphoma[29].

Therapeutic intervention-induced cytokine storm. Immune-modulating therapies, including CAR T cell therapy, antibodies and bispecific T cell engagers, have become a mainstay of therapy for many malignancies, especially haematological malignancies. CAR T cell therapy and other T cell-engaging therapies can induce robust cytokine release and cause a form of cytokine storm called CRS[31]. Although the incidence and frequency of CRS following CAR T cell therapy can vary by CAR construct and disease type, the severity of CRS is most notably associated with disease burden[32–34]. In early trials of CAR T cell therapies, studies reported an incidence of CRS of 88–93%, with high rates of severe (grade ≥3) CRS[35,36]. However, over time, CAR T cell treatments have been used earlier in cancer treatment when the disease burden is lower, which makes the treatment less inflammatory. Furthermore, the management strategies for CRS have improved through clinical trials, leading to a substantial decrease in the incidence of severe CRS[37–40]. In post-marketing surveillance, rates of CRS are reported to be ~50%[41].

Overall, the true incidence of cytokine storm remains difficult to assess, and the current increases in incidence likely reflect a combination of increased awareness of the condition and increases in the frequency of the underlying conditions that drive cytokine storm. Identification of patient populations at risk remains a critical area for future investigation to perform mechanistic characterizations of the cytokines involved and to implement appropriate treatment strategies. Additionally, not all individuals exposed to the same stimuli will develop cytokine storm. Genetic differences can contribute to this susceptibility, further complicating epidemiological analysis[42–44]. For example, in sJIA, patients with elevated circulating levels of IL-18 owing to activating mutations in inflammasome sensors, such as *NLRC4* and *NLRP3*, show increased propensity for developing cytokine storm or MAS[43,44]. Therefore, cytokine storm arises from a complex interplay between environmental triggers and an individual's inherited immune-regulatory architecture, further emphasizing the critical need to understand its epidemiology and molecular mechanisms for therapeutic development.

Mechanisms/pathophysiology

Although the upstream clinical conditions that lead to cytokine storm can vary, shared immune signalling pathways are generally responsible for the cytokine production and inflammatory outcomes. Cytokine storm begins with cytokine release as a result of innate immune cells recognizing pathogens, PAMPs or DAMPs in their natural response to infection or localized disruptions in homeostasis. This sensing initiates a cascade of inflammatory signalling pathways, including NF-κB and lytic, inflammatory cell death signalling, which can produce and further release inflammatory cytokines, chemokines, alarmins and DAMPs[1]. Under normal conditions, the innate immune system efficiently resolves inflammation and restores homeostasis, with the short half-lives of cytokines limiting their effects to the inflammation site and minimizing systemic impacts. However, elevated cytokine levels in the

circulation can drive paracrine signalling that causes further cytokine production in immune cells and non-immune cells, as well as inflammatory cell death, disrupted immune homeostasis, and damage to vital tissues and organs[1–3,20]. Under these conditions of aberrant elevated cytokines, cytokine storm occurs.

Temporal progression of cytokine storm

Cytokine storm can be summarized by a temporal progression from onset to amplification to peak or crisis, and finally to resolution of the immune response or failure of resolution. The exact timing and progression vary across conditions; however, these four overlapping phases have generally been delineated[45] (Fig. 2). In the onset phase (hours to days 1–2), pathogens, PAMPs and DAMPs engage innate immune sensors, leading to pro-inflammatory cytokine production and release through secretion pathways or via inflammatory, lytic cell death such as pyroptosis and PANoptosis. In the amplification phase (days 2–5), progressive activation of macrophages and neutrophils, along with recruitment of T helper 1 (T_H1)–T_H17 lymphocytes, intensifies the release of cytokines and complement (for example, C3a and C5a)[46] as well as the induction of inflammatory cell death (PANoptosis), exacerbating vascular permeability, driving tissue infiltration and perpetuating a feedforward inflammatory circuit[47,48]. For patients that progress to the peak or crisis phase (days 5–10), systemic manifestations become severe, including acute respiratory distress syndrome (ARDS), cytopenia, coagulopathy and multiorgan dysfunction. Excessive DAMP and cytokine release activate platelets, endothelial cells, and both innate and adaptive immune cells, driving pro-coagulatory cascades and endothelial injury[49]. Finally, in the resolution phase or failure phase, the immune system either gradually contracts, with immune cells being cleared from the body, or progresses towards immune paralysis, where immune cells can no longer respond effectively to stimuli and perform their critical host defence functions[50–52] (Fig. 2).

Role of immune cells

Excessive and uncontrolled cytokine release triggers cytokine storm and drives the onset and amplification phases to the peak of disease (Fig. 2). The specific cytokine milieu varies depending on the precipitating condition, and current evidence suggests that IL-1 family cytokines (such as IL-1β and IL-18), IL-6, TNF and IFNγ are likely the most important drivers of the condition[53]. Both innate and adaptive immune cells

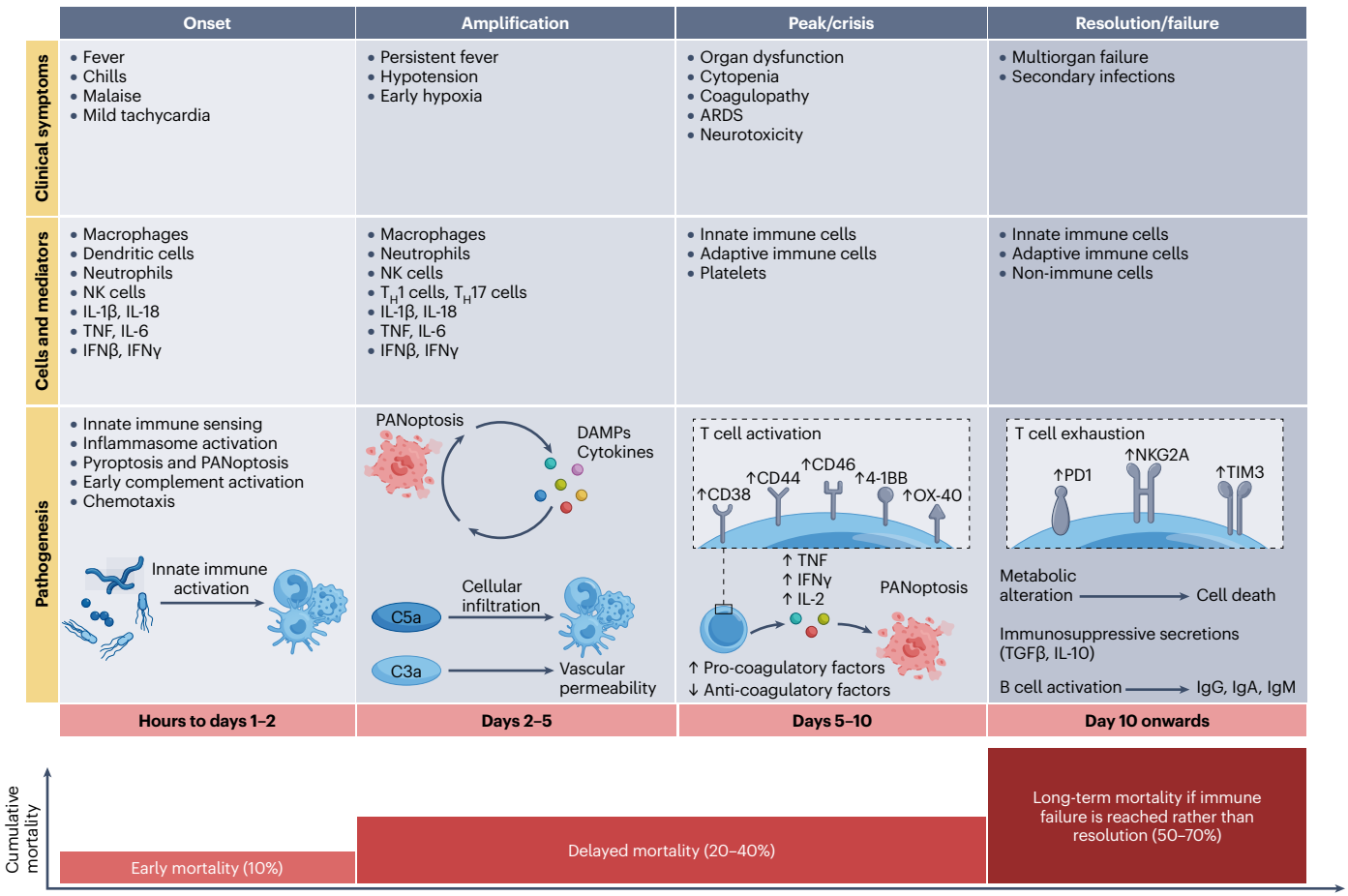

Fig. 2 | Temporal progression of immune and pathophysiological events in cytokine storm. The schematic outlines the four major stages of cytokine storm pathogenesis – onset, amplification, peak/crisis, and resolution/failure – integrating clinical symptoms, cellular mediators and immunopathological mechanisms over time. The cumulative mortality indicates the percentage of patients expected to succumb to cytokine storm-induced complications if the disease reaches each stage, with the long-term mortality reflecting mortality if immune failure occurs rather than resolution. ARDS, acute respiratory distress syndrome; DAMPs, damage-associated molecular patterns; NK, natural killer; T_H, T helper.

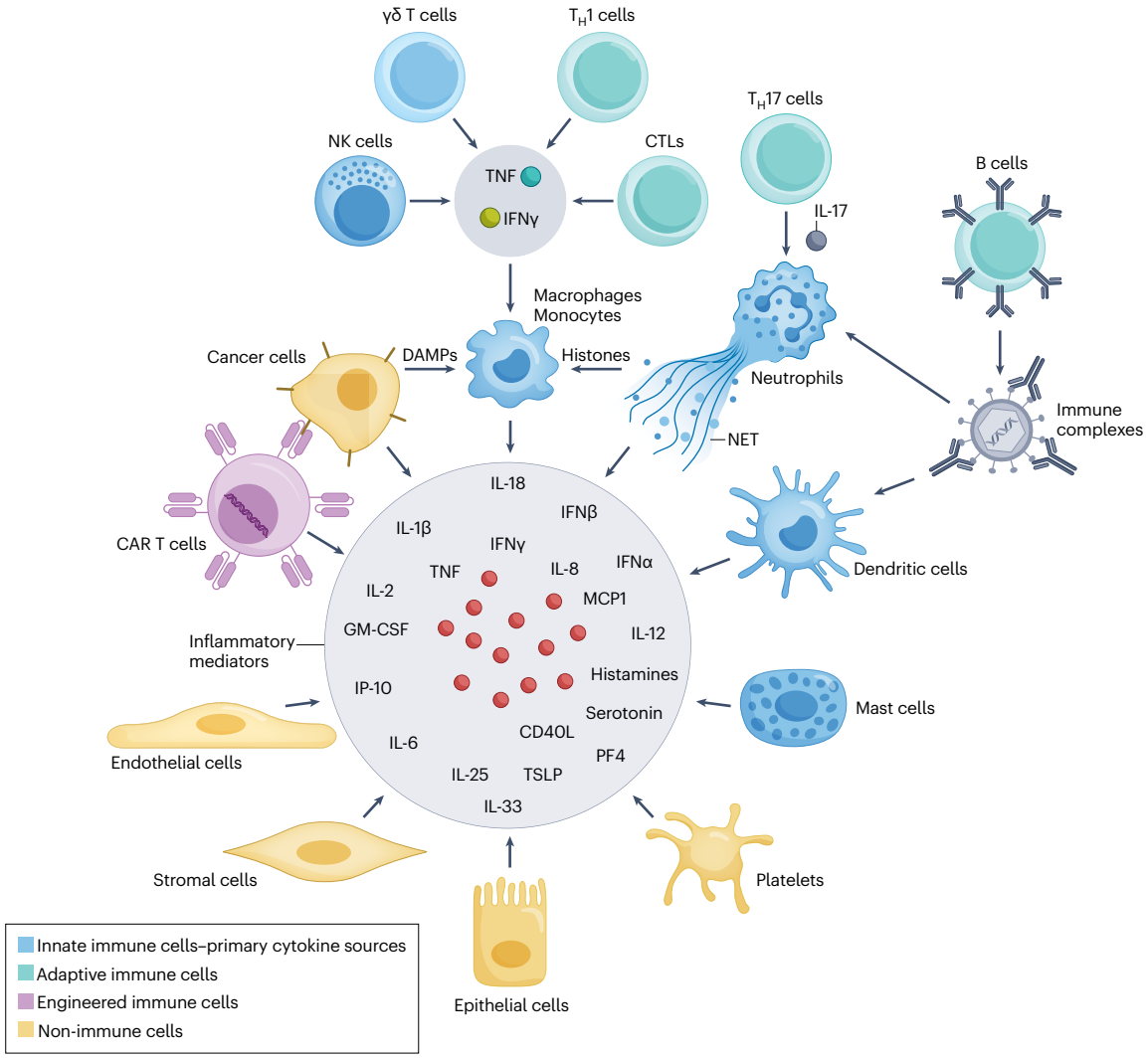

Fig. 3 | Cellular and cytokine networks in cytokine storm. In cytokine storm, there is a complex interplay among innate, adaptive, engineered and non-immune cells contributing to cytokine storm and systemic inflammation. Innate immune cells – macrophages, monocytes, dendritic cells, neutrophils, natural killer (NK) cells and mast cells – serve as primary cytokine sources. Activated neutrophils release histones and neutrophil extracellular traps (NETs), whereas macrophages and monocytes secrete damage-associated molecular patterns (DAMPs) that perpetuate inflammation. Adaptive immune cells – T helper 1 (T_H1), T_H17, γδ T cells, cytotoxic T lymphocytes (CTLs) and B cells – amplify responses through cytokines such as IFNγ, IL-17 and IL-2, promoting cross-activation of myeloid and stromal cells. Engineered immune cells (for example, chimeric antigen receptor (CAR) T cells) and non-immune cells (such as endothelial, epithelial, and stromal cells and platelets) further enhance inflammation via secretion of IL-25, IL-33, TSLP and PF4, contributing to vascular permeability and coagulopathy. Collectively, these cellular interactions form a cytokine network – centred on TNF, interferons, IL-1β, IL-6 and chemokines (for example, IP-10, MCP1) – that drives immune hyperactivation, tissue injury and multiorgan dysfunction characteristic of cytokine storm. GM-CSF, granulocyte–macrophage colony-stimulating factor.

are linked to cytokine storm-associated diseases and can contribute to this cytokine release (Fig. 3). Innate immune cells are commonly implicated in the onset phase of cytokine storm, whereas adaptive immune cells sustain inflammation and non-immune cells contribute to cytokine production at later phases (Figs. 2 and 3). Following production, cytokine release can occur as a result of inflammatory, lytic cell death or through non-lytic cytokine release pathways such as the canonical and non-canonical secretory pathways[54,55].

Innate immune cells. Excessive cytokine production that drives cytokine storm is generally initiated by innate immune cells, including macrophages, monocytes, neutrophils, dendritic cells, natural killer cells, mast cells and γδ T cells (Figs. 2 and 3). These cells express a diverse repertoire of membrane-bound and cytosolic pattern-recognition receptors to detect PAMPs, DAMPs, cytokines and homeostatic disruptions. Activation of Toll-like receptors (TLRs) by bacterial or viral PAMPs or DAMPs triggers MyD88-mediated and TRIF-mediated signalling pathways, such as NF-κB, p38, JNK, AP-1 and interferon signalling, leading to transcriptional upregulation of inflammatory cytokines, including IL-6, TNF and IL-1 family cytokines. Among these, the IL-1 family cytokines IL-1β and IL-18 require inflammasome activation for their maturation and release. Inflammasomes

are multi-protein complexes comprising a sensor (for example, NLRP3, AIM2, NLRC4, pyrin and NLRP1)[8], the adaptor ASC and the effector protease caspase 1, which cleaves IL-1β and IL-18 to their active forms[56]. Mutations in genes encoding inflammasome sensors, such as *NLRP3*, *MEFV* and *NLRC4*, result in constitutive or hyperactive inflammasome assembly, leading to excessive IL-1β and IL-18 release[57]. These mutations are also strongly linked to systemic auto-inflammatory diseases, including cryopyrin-associated periodic syndromes, familial Mediterranean fever and MAS[57]. Additionally, IL-1 family cytokines have emerged as key mediators of hyperinflammation, particularly in conditions such as COVID-19 and sJIA, in which cytokine storm occurs[58]. Elevated levels of circulating IL-18 have been consistently observed in patients with adult-onset Still disease or sJIA who develop cytokine storm[59], and IL-1 has been implicated in rare cases of multi-system inflammatory syndrome in children following COVID-19 (refs. 60,61). However, clinical trials evaluating IL-1 blockade in severe COVID-19 have reported inconclusive results, with limited improvement in mortality[62–64], suggesting that cytokines beyond the IL-1 family also contribute to the cytokine storm pathology. This finding is further supported by studies showing critical roles for interferons, TNF, IL-6 and other cytokines in cytokine storm pathology[1,2,64,65].

At the cellular level, monocytes and tissue-resident macrophages are the major contributors to the onset phase of cytokine storm by releasing large quantities of IL-1β, IL-6 and TNF (Fig. 3), which drive paracrine cell death, systemic inflammation, and organ dysfunction and failure. For example, in HLH and MAS, macrophages are hyperactivated, leading to haemophagocytosis, cytopenias and excessive cytokine production[65] (Fig. 3). In addition to these cells, several other innate immune cells also release cytokines in context-dependent manners. In COVID-19, natural killer cells and innate-like γδ T cells contribute to cytokine storm by secreting high levels of IFNγ and TNF[66]. These cytokines synergistically trigger inflammatory cell death and exacerbate tissue damage as observed in preclinical models of SARS-CoV-2 infection, sepsis and HLH[2] (Fig. 1). Additionally, in COVID-19, plasmacytoid dendritic cells infiltrate the lungs and activate macrophages to amplify cytokine storm[67].

Beyond the innate immune cells that directly produce cytokines, neutrophils also contribute to cytokine storm by promoting inflammation, tissue damage and thrombosis through dysregulated NETosis (release of neutrophil extracellular traps (NETs) that are meant to clear infections). In sepsis and COVID-19, excessive NET components, including DNA and histones, act as DAMPs, inducing inflammatory cell death and contributing to coagulopathy and ARDS[68–71]. In SLE, NETs serve as auto-antigens that sustain immune activation, leading to the release of cytokines such as IL-1β and type I interferons (for example, IFNα) by plasmacytoid dendritic cells[72,73] (Fig. 3). Therapeutic approaches targeting extracellular histones have shown promise in reducing organ damage in sepsis[68,74,75].

Adaptive immune cells. Adaptive immune cells, although less implicated than innate immune cells in the onset phase of cytokine storm, have critical roles in perpetuating inflammation and exacerbating disease severity through the amplification and peak phases by contributing to excess cytokine release (Fig. 2).

Overactivation of $CD4^+$ T cells, particularly the T_H1 and T_H17 cell subsets, drives cytokine release and tissue damage in severe COVID-19, HLH and autoimmune diseases[76–78]. T_H1 cells secrete large amounts of IFNγ, whereas T_H17 cells release IL-17, both of which contribute to cytokine storm by activating macrophages and recruiting neutrophils[79] (Fig. 3). $CD8^+$ cytotoxic T lymphocytes exacerbate tissue damage in viral infections like influenza and severe COVID-19 by releasing cytokines such as TNF and IFNγ[80] (Fig. 3). The killing of infected cells by cytotoxic T lymphocytes also releases various PAMPs and DAMPs, which can be sensed by pattern-recognition receptors on innate immune cells to perpetuate further cytokine release. Additionally, dysregulated regulatory T cells fail to suppress excessive immune responses, allowing the storm to persist in COVID-19 and autoimmune conditions like SLE and type 1 diabetes mellitus[81,82].

Although B cells are not direct drivers of cytokine storm, they contribute to diseases like SLE and COVID-19 by producing auto-antibodies[83,84]. These auto-antibodies form immune complexes that activate macrophages and neutrophils via Fc receptors and the complement system, indirectly promoting cytokine release. In SLE, immune complexes activate plasmacytoid dendritic cells through TLR9, leading to excessive IFNα production and tissue damage[83] (Fig. 3). B cell hyperactivation has also been linked to the secretion of IL-6 and TNF[85]. Notably, depletion of B cells via anti-CD20 therapy has been effective in reducing cytokine production in conditions such as human herpesvirus 8 (HHV8)- and HIV-associated multicentric Castleman disease[86,87].

Adaptive and innate immune cell mechanisms of cytokine production can also be intrinsically linked. For instance, in CAR T cell therapy, cytokine storm is often triggered by the rapid killing of tumour cells, which releases DAMPs such as DNA, RNA, HMGB1 and ATP. These DAMPs activate pattern-recognition receptors on innate immune cells, stimulating the production of IL-6, TNF, IFNγ and IL-1β[88] (Fig. 3).

Cytokine storm amplification

The initial cytokine release that precipitates cytokine storm can occur as a result of either cellular signalling that drives cytokine production and release or the execution of inflammatory cell death, which induces the formation of membrane pores for cytokines to leak out. At the cellular level, multiple lytic cell death pathways, including pyroptosis and PANoptosis, can contribute to the release of cytokines, and both have been associated with cytokine release for cytokine storm[2,42,89–91]. Once cytokine production is initiated, the short half-lives of most cytokines are meant to ensure the timely resolution of inflammation. However, in the case of cytokine storm, chronically elevated cytokine levels can disrupt immune homeostasis[2] and serve as danger signals that are directly detected by innate immune sensors on neighbouring cells. The innate immune sensors engaged by cytokines can induce paracrine PANoptosis, resulting in inflammatory cell death in cells exposed to cytokines, which further perpetuates cytokine release (Fig. 4). This process forms a self-amplifying loop that drives persistent immune activation and systemic tissue injury[1,2] (Fig. 1). Tissue damage and pathology in cytokine storm are associated with cytokine-mediated damage at multiple sites, including cytokine-mediated damage to the vascular endothelium, resulting in oedema throughout the body and causing organ dysfunction[92]; cytokine-mediated lung injury, causing alveolar disruption and reduced gas exchange[93]; cytokine-mediated disruptions in bone marrow function and haematopoietic stem cell renewal[94,95]; cytokine-mediated immune cell recruitment to organs, where they can directly cause damage[96]; and the loss of critical cells due to the induction of cytokine-mediated cell death through PANoptosis[1,2].

PANoptosis and inflammatory cell death. PANoptosis is a lytic innate immune cell death pathway initiated by innate immune sensors and

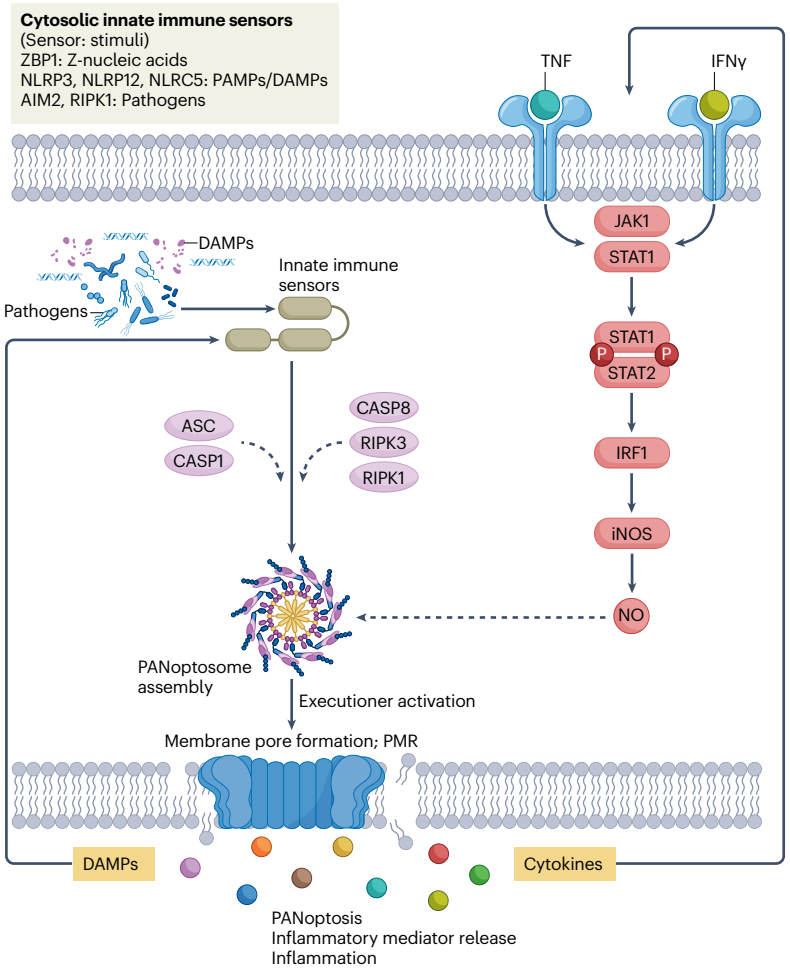

Fig. 4 | Innate immune sensors and PANoptosis in cytokine storm amplification. Innate immune sensing and PANoptosome assembly induce PANoptosis to drive further cytokine and damage-associated molecular pattern (DAMP) release and inflammation. Upon sensing pathogen-associated molecular patterns (PAMPs) and DAMPs, certain cytosolic sensors assemble a multi-protein complex known as the PANoptosome by recruiting key cell death regulators, including caspases (CASP) and receptor-interacting protein kinases (RIPKs). Caspase 8 (CASP8) is a key regulatory molecule in this process. After complex formation and activation, PANoptosis, an inflammatory form of innate immune cell death, is triggered, leading to the activation of a network of pore-forming and membrane-damaging molecules. This membrane damage releases cytosolic contents and inflammatory mediators, which can further perpetuate PANoptosis and inflammation. Specific endogenous and pathogen-derived molecules serve as triggers for PANoptosome formation, including Z-nucleic acids (sensed by ZBP1), PAMPs and DAMPs (sensed by NLRP3, NLRP12 and NLRC5), and pathogens such as HSV1 and *Francisella* (sensed by AIM2) or *Yersinia* (sensed by RIPK1). Additionally, the synergistic action of TNF and IFNγ activates the JAK–STAT1 signalling pathway, leading to upregulation of IRF1 and inducible nitric oxide synthase (iNOS) that triggers nitric oxide (NO) production to act as a key driver of PANoptosis. PMR, plasma membrane rupture.

driven by caspases and receptor-interacting protein kinases (RIPKs). In response to pathogens, PAMPs, DAMPs and homeostatic disruptions, innate immune sensors can activate to form a PANoptosome complex that drives the execution of cell death (PANoptosis) and the release of cytokines and DAMPs[97] (Fig. 4). Furthermore, cytokines themselves can activate innate immune sensors to drive PANoptosis[2]. Studies have identified several PANoptosome-forming innate immune sensors[8,98], with the nucleic acid sensor ZBP1 being the first identified[99,100] (Fig. 4). ZBP1 was initially characterized as the innate immune sensor of influenza A virus[99] that can drive NLRP3 inflammasome activation, IL-1β and IL-18 production, and inflammatory cell death and PANoptosis. Additional research has shown that ZBP1 can also form a PANoptosome and drive cell death during SARS-CoV-2 infection[101] as well as during tumour immunity[102]. Furthermore, ZBP1 has been implicated in several auto-inflammatory disorders owing to its regulation by the RNA-editing enzyme ADAR1 (ref. 103). In homeostasis, ZBP1 and ADAR1 interact with each other to inhibit ZBP1-mediated PANoptosis[102,103]. Mutations in *ADAR1* lead to abnormal type I interferon production, heightened interferon-stimulated gene (ISG) expression, accumulation of endogenous Z-nucleic acids, and chronic systemic inflammation and are associated with diseases such as Aicardi–Goutieres syndrome, SLE and bilateral striatal necrosis[103]. The pathology in these conditions may be attributed to the failure of ADAR1 to block ZBP1-mediated PANoptosis[102].

Studies have identified several other PANoptosome sensors. NLRC5 and NLRP12 form a PANoptosome, with the NLRP3 inflammasome as an integral component, to drive cell death as well as DAMP and cytokine release in response to haem and PAMPs or TNF[8,104,105] (Fig. 4). This signalling complex likely amplifies systemic inflammation in conditions associated with haemolysis, such as SLE, infection and autoimmune diseases, where the haem released by haemolysis serves as a potent DAMP[8,104,105]. RIPK1 and AIM2 also assemble PANoptosomes to mediate inflammatory cell death in response to pathogens, with RIPK1 responding to *Yersinia*[106] and AIM2 responding to *Francisella* and herpes simplex virus 1 (HSV1)[107] (Fig. 4). NLRP3 has also been identified as a PANoptosome sensor[108].

Cytokines and PANoptosis — amplification loop. Although innate immune sensors regulate the upstream activation of PANoptosis, the shared downstream outcome is caspase 8 activation, along with activation of other caspases and RIPKs, followed by cellular lysis and plasma membrane rupture, often involving a network of executioners and NINJ1 (refs. 109,110); this process releases cytokines and DAMPs to perpetuate further inflammation (Figs. 1 and 4). Once cytokines have been released, whether because of lytic cell death or through other signalling pathways (for example, NF-κB, p38, JNK, AP-1 and interferon signalling), the cytokines themselves can also drive paracrine

PANoptosis. Molecularly, TNF and IFNγ together activate JAK1–STAT1 signalling to upregulate IRF1, which in turn induces inducible nitric oxide synthase to produce nitric oxide. This increase in nitric oxide activates caspase 8 and RIPK3-mediated PANoptosis[2] (Fig. 4). TNF and IFNγ seem to be sufficient to drive cytokine storm, as intraperitoneal injection of these cytokines induces mortality in mice[2,111] and mirrors the major symptoms of cytokine storm observed in patients with COVID-19 (ref. 2). Extracellular ISG15, released from macrophages in response to SARS-CoV-2 papain-like protease (PLpro), amplifies inflammation by engaging the TNF and IFNγ feedforward loop that drives immunopathology in COVID-19 (ref. 112). Furthermore, neutralization of TNF and IFNγ is effective in improving cytokine storm symptoms in preclinical models of COVID-19, septic shock and HLH[2].

Collectively, the activation of PANoptosis and cytokine release form a feedforward loop to perpetuate inflammation and drive cytokine storm pathogenesis. This process forms the molecular basis for cytokine storm (Fig. 1).

Diagnosis, screening and prevention

Signs and symptoms

As discussed above, cytokine storm is an umbrella term encompassing several life-threatening clinical syndromes. Hence, the symptoms, severity, onset and duration of cytokine storm vary greatly. The clinical presentation of cytokine storm also varies depending on the underlying aetiology, disease triggers and treatments administered to the patient[113]. Despite variability in the initial pathological processes, the later phases of cytokine storm often converge into a similar set of clinical manifestations.

The symptoms of cytokine storm typically begin with nonspecific systemic signs such as persistent fever, fatigue, anorexia, headache and, in some cases, diarrhoea, arthralgia, myalgia and neuropsychiatric symptoms (for example, confusion, agitation or mood changes)[3] (Fig. 5). These symptoms may result from tissue damage and acute physiological changes caused directly by cytokines or symptoms may be caused by immune cells sensing and responding to the cytokines. Additionally, acute liver injury and central nervous system involvement, manifesting as encephalopathy or seizures, are common early features of severe cytokine storm, reflecting the high metabolic and vascular sensitivity of these organs to systemic inflammation[114]. Without prompt and aggressive treatment, patients can progress rapidly to severe complications, including disseminated intravascular coagulation, hypotension, dyspnoea and hypoxaemia, and vasodilatory shock. Renal failure and cardiomyopathy tend to occur later in the disease course as well, secondary to sustained cytokine exposure, haemodynamic instability and multiorgan stress. Many patients also show respiratory symptoms like coughing and rapid breathing, which can develop into ARDS (Fig. 5). Therefore, early diagnosis of cytokine storm — to provide treatment before severe complications begin — will be lifesaving.

Laboratory findings

The laboratory findings in cases of cytokine storm vary based on the underlying aetiology but share common features consistent with

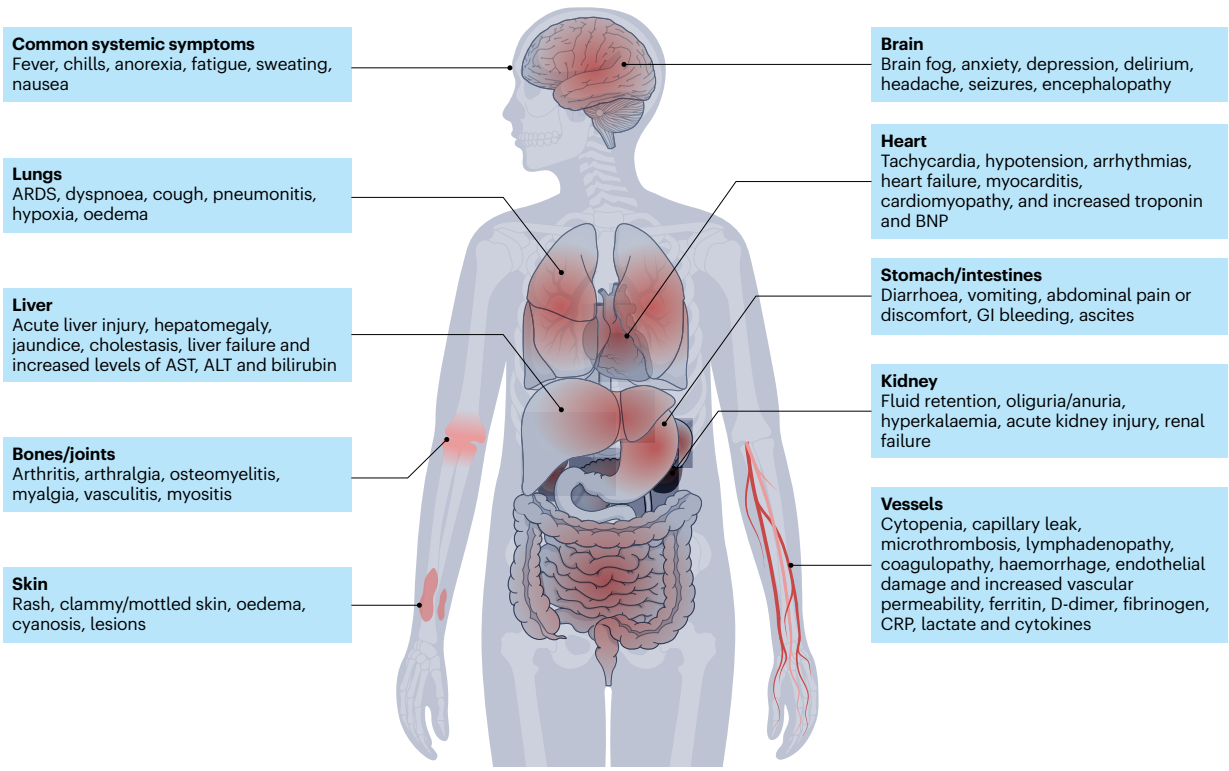
Common systemic symptoms
Fever, chills, anorexia, fatigue, sweating, nausea
Lungs
ARDS, dyspnoea, cough, pneumonitis, hypoxia, oedema
Liver
Acute liver injury, hepatomegaly, jaundice, cholestasis, liver failure and increased levels of AST, ALT and bilirubin
Bones/joints
Arthritis, arthralgia, osteomyelitis, myalgia, vasculitis, myositis
Skin
Rash, clammy/mottled skin, oedema, cyanosis, lesions
Brain
Brain fog, anxiety, depression, delirium, headache, seizures, encephalopathy
Heart
Tachycardia, hypotension, arrhythmias, heart failure, myocarditis, cardiomyopathy, and increased troponin and BNP
Stomach/intestines
Diarrhoea, vomiting, abdominal pain or discomfort, GI bleeding, ascites
Kidney
Fluid retention, oliguria/anuria, hyperkalaemia, acute kidney injury, renal failure
Vessels
Cytopenia, capillary leak, microthrombosis, lymphadenopathy, coagulopathy, haemorrhage, endothelial damage and increased vascular permeability, ferritin, D-dimer, fibrinogen, CRP, lactate and cytokines

Fig. 5 | Clinical manifestations and organ-specific complications associated with cytokine storm. This illustration summarizes the major organ system dysfunctions and clinical features that arise from widespread immune dysregulation, endothelial injury and cytokine-mediated inflammation during cytokine storm. ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; AST, aspartate transaminase; BNP, B-type natriuretic peptide; GI, gastrointestinal.

systemic inflammation. However, no specific biomarkers currently exist. A hallmark of cytokine storm, as highlighted in its definition, is the release of inflammatory markers in the systemic circulation. Routine nonspecific inflammatory markers are also generally elevated in cytokine storm. CRP, a liver-produced acute-phase reactant, is consistently increased in the circulation, and its concentration correlates with disease severity[115]. Patients with cytokine storm also frequently exhibit hypertriglyceridaemia and blood-count abnormalities, including leukopenia, leukocytosis, thrombocytopenia and anaemia. This process can be accompanied by elevated D-dimer and low fibrinogen concentrations[116].

Evidence suggests that the changes in circulating cell numbers may be caused by a complex interplay between cytokine-induced production and mobilization of immune cells from bone marrow progenitors, immune-mediated lysis of the cells (for example, red blood cell lysis leading to thrombotic microangiopathy) and chemokine-induced migration[3]. The presence of thrombocytopenia is most likely a combination of poor bone marrow production (owing to leukaemic infiltration), peripheral consumption in enlarged spleen or liver, or disseminated intravascular coagulation or thrombotic microangiopathy. Cytokine storm often presents features of (sub)clinical disseminated intravascular coagulation; therefore, relative thrombocytopenia is an important diagnostic clue.

Among inflammatory markers, one of the most specific markers for diagnosing cytokine storm is a disproportionately high circulating concentration of ferritin, which is an iron-binding protein primarily released by activated macrophages as well as hepatocytes and other cells[117]. Although no specific diagnostic threshold for ferritin in cytokine storm has been described, very high concentrations should trigger an assessment for cytokine storm[118]. For example, in patients with Still-associated MAS, median ferritin circulating concentrations were >5,000 ng/ml (ref. 119).

Additionally, circulating concentrations of cytokines that contribute to disease pathogenesis are elevated in patients with cytokine storm. In CAR T cell-induced cytokine storm, IL-6 and the T cell activation marker soluble IL-2 receptor-α (sIL-2Rα) chain, also termed sCD25, are increased, and molecules in the interferon pathway, including IFNγ and the interferon-inducible chemokines CXCL9 and CXCL10, are also elevated[120]. Increased IFNγ activity, mirrored by high circulating concentrations of CXCL9, has also been reported in patients with Still disease associated with MAS[121]. IL-18, a strong inducer of IFNγ, is also very high in the circulation of patients with MAS[122]. Excessive T cell activation in the cytokine storm associated with Kawasaki disease is accompanied by high concentrations of sIL-2R as well as the increased production of IL-17 (ref. 123). However, no standard cytokine profile is currently available that can be used to predict cytokine storm[3]; this lack of markers is a major limitation of current screening and diagnostic procedures.

For additional diagnostic assessment, haemophagocytosis has been described as a specific characteristic of MAS or cytokine storm; however, bone marrow biopsy is not often performed owing to low sensitivity and specificity[25]. The circulating concentrations of transaminases are often increased and can help the diagnosis as hepatitis occurs during some forms of cytokine storm[124]. Additional diagnostic investigations in patients with cytokine storm can include imaging directed to detect enlarged liver, spleen and lymph nodes, which allows the assessment of end organ involvement.

Overall, given the varied laboratory findings from patient to patient, currently, no standardized set of diagnostic criteria is available that can be applied to cytokine storm.

Screening and prevention

As cytokine storm generally results from an underlying clinical condition, diagnosing the cause is critical. However, diagnosis can be challenging based on clinical features alone, given the overlapping clinical presentation across all types of cytokine storm. Physicians consider the patient's underlying medical condition, which might already be known or may require its own diagnosis. A patient may need to be diagnosed with a genetic disorder, autoimmune or auto-inflammatory condition, or infection, necessitating various medical tests.

Distinguishing cytokine storm caused by iatrogenic factors, such as CAR T cell therapy, from cytokine storm owing to systemic infections or auto-inflammatory conditions is crucial, as the clinical management strategies will be different. Cytokine storm is often encountered in patients who display a dysregulated, exaggerated immune response during viral infections and, therefore, the potential diagnosis of viral infections such as Epstein–Barr virus, cytomegalovirus, adenovirus, HHV6, HHV8, human immunodeficiency virus, or SARS-CoV-2 is particularly important for addressing the aetiological cause of the syndrome[125,126]. Similarly, cytokine storm can be encountered in patients with autoimmune diseases (for example, SLE) or haematological malignancies (for example, lymphoma and leukaemia)[28,30]. Therefore, a complete work-up for infection, along with laboratory assessments of kidney and liver function, should be performed in all suspected cases[3].

The various challenges in screening and diagnosis make it difficult to provide early treatment, which is often critical for patient improvement. Therefore, many clinical strategies are focused on prevention. As many cases of cytokine storm are induced by pathogens, avoiding infection and maintaining microbiome homeostasis are associated with a reduced risk of cytokine storm[127–129]. Other preventive measures can also be beneficial. In the case of cytokine storm induced by bacterial infections, CAR T cells, and other T cell-activating therapies, catecholamine levels can dramatically increase, leading to an increase in the production of IL-6 and other cytokines, and enhancing inflammatory injury[130]. Treatment with the tyrosine hydroxylase antagonist metyrosine can reduce catecholamine levels and cytokine responses, substantially increasing survival in mice challenged with various inflammatory stimuli[130]. Similar protection against hyperinflammatory stimuli is observed with adrenergic receptor antagonists, which suggests potential for this drug class to prevent cytokine storm[131]. One retrospective clinical study showed that patients who are hospitalized and diagnosed with pneumonia or ARDS are significantly less likely to require mechanical ventilation and have reduced mortality if they took adrenergic receptor antagonists during the year preceding hospitalization[132]. In the case of therapeutic intervention-induced cytokine storm, drug screening methods may help to predict patients more likely to develop cytokine storm in response to certain drugs, although current methods have yet to reliably predict such outcomes. For individuals receiving immunotherapy, evaluating the patient and modulating the medication dosage may reduce the risk of cytokine storm.

Overall, the screening and prevention of cytokine storm still face major limitations in the clinic, and future advances in screening technologies will be needed to identify patients who are at risk for developing cytokine storm.

Management

The management of cytokine storm generally focuses on identifying the underlying disorder that caused the initial immune dysregulation, assessing the severity of the patient's clinical condition, and deciding

Table 1 | Therapeutics in cytokine storm — targeted treatments for cytokine pathways

Target	Anti-IL-1	Anti-IL-18	Anti-IL-6/IL-6R	Anti-TNF	Anti-IFNγ	Anti-JAK	Refs.
Drugs	Anakinra Canakinumab Rilonacept MAS825	Tadekinig-α	Tocilizumab Siltuximab Sarilumab	Adalimumab Certolizumab Etanercept Golimumab Infliximab	Emapalumab	Baricitinib Tofacitinib Upadacitinib Ruxolitinib	
Mixed responses or ongoing clinical trials	Sepsis COVID-19 CAR T cell therapy Giant cell arteritis Gout Psoriasis sJIA MAS	sJIA Adult Still disease NLRC4–MAS	GvHD Sepsis	Sepsis COVID-19	COVID-19 Crohn's disease	SLE HLH Crohn's disease Psoriasis	43,64,163, 164,181–203
FDA-approved drugs (any indication) with efficacy in the given setting	sJIA Adult Still disease Rheumatoid arthritis CAPS FMF	None	sJIA Castleman disease CAR T cell therapy Rheumatoid arthritis Giant cell arteritis COVID-19	Rheumatoid arthritis Crohn's disease Ulcerative colitis Psoriasis Refractory asthma	Adult Still disease	COVID-19 sJIA GvHD Rheumatoid arthritis Ulcerative colitis	26,160,165, 173,204–227

CAPS, cryopyrin-associated periodic syndromes; CAR, chimeric antigen receptor; GvHD, graft-versus-host disease; FMF, familial Mediterranean fever; HLH, haemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; sJIA, systemic juvenile idiopathic arthritis; SLE, systemic lupus erythematosus.

the appropriate treatment based on the aetiology and severity (Table 1). Here, we focus primarily on the therapeutic approaches that target cytokine storm itself, rather than the underlying disease. Early intervention is often considered critical to minimizing the tissue damage and potential organ failure that can result from cytokine storm. The lack of clear diagnostic criteria or cytokine thresholds makes early treatment difficult. Several groups of medications can be considered for the treatment of cytokine storm, as also detailed in the official recommendation documents of the American College of Rheumatology–European League Against Rheumatism consensus report on MAS[133].

Glucocorticoids

Glucocorticoids are potent anti-inflammatory drugs that inhibit multiple inflammatory pathways, including NF-κB signalling, the synthesis of pro-inflammatory cytokines and chemokines, and lymphocyte proliferation. At the same time, glucocorticoids can enhance the production of anti-inflammatory cytokines such as IL-10 or IL-1Ra[134]. Owing to their potent anti-inflammatory effects, glucocorticoids represent a crucial component in the treatment of cytokine storm. Treatment is usually started through daily intravenous 'pulse' therapy of methyl-prednisolone for 3 days, followed by a lower dose of the drug[135]. Dexamethasone is an alternative glucocorticoid preparation that can be used, and it has been recommended for cytokine storm associated with primary HLH[136,137]. The duration of treatment with glucocorticoid therapy depends on the clinical progression of the disease in each patient but usually extends for 4–8 weeks.

Corticosteroids seem to be most beneficial for people with cytokine storm owing to underlying autoimmune diseases[138]. However, whether a corticosteroid is the best option for people with cytokine storm from other causes is not clear. Corticosteroids may blunt the therapeutic effect of CAR T cells and increase susceptibility to post-treatment infections[139,140]. Therefore, more specific, targeted therapies are often considered.

Cytokine inhibitors

Targeted therapies that block circulating cytokines are frequently used in the management of cytokine storm (Table 1). One of the major pathophysiological pathways in cytokine storm is the elevated bioactivity of IL-1, and inhibitors of this pathway decrease hyperinflammation in auto-inflammatory syndromes as well as common inflammatory diseases[141]. The first specific inhibitor developed to target the IL-1 pathway is anakinra – a recombinant IL-1 receptor antagonist with a short half-life so as to limit the increased risk of infection that can be an adverse effect. Randomized trials with anakinra to manage cytokine storm have been conducted in COVID-19, and anakinra has demonstrated beneficial effects in patients with COVID-19 and severe hyperinflammation identified via high circulating concentrations of soluble urokinase plasminogen activator receptor[63]. In addition, extensive observational studies support the use of anakinra in cytokine storm associated with other diseases[135]. Furthermore, anakinra has been especially used in the treatment of cytokine storm associated with Still disease, where the role of IL-1 pathways in the pathophysiology is well documented. This therapeutic approach often requires higher dosing than the typical amounts prescribed, and may be complemented with glucocorticoids to achieve adequate control of hyperinflammation[142]. In addition, anakinra has been suggested for use in the treatment of sepsis-associated cytokine storm. A post hoc analysis of an earlier anakinra trial in sepsis suggested that the treatment would have been successful if patient stratification had been applied based on cytokine storm criteria[143]. This conclusion is supported by the results of the small randomized PROVIDE trial of anakinra in sepsis-induced cytokine storm[144], which is the basis of the larger phase IIb Immunosep trial testing the use of anakinra in cytokine storm associated with sepsis[145]. Studies have also shown that anakinra alleviates hypercytokinaemia in sJIA and COVID-19 (refs. 146,147). In addition, the monoclonal anti-IL-1β antibody, canakinumab, can inhibit IL-1 bioactivity. However, canakinumab has several disadvantages – it

inhibits only IL-1β and not IL-1α, its long half-life may be deleterious in serious conditions, and it has poorer central nervous system penetration. The cost of canakinumab is also much higher than that of anakinra, which limits its use, although some studies reported beneficial effects[148].

The role of IL-6 blockade in cytokine storm treatment is less well studied, with the exception of CAR T cell therapy-induced cytokine storm and in severe hyperinflammatory forms of COVID-19. Tocilizumab, an anti-IL-6R antibody, is frequently used in CRS downstream of CAR T cell therapy, where IL-6 is known to drive clinical manifestations. However, tocilizumab lacks efficacy for cytokine-related neurotoxicity, as it is not known to cross the blood–brain barrier[149]. Additional strategies to mitigate the risk of cytokine storm by modifying the CAR T cells to include transgenic cytokine release cassettes are also being investigated[150]. Clinical trials involving anti-IL-6R therapy, such as tocilizumab (also in combination with dexamethasone), have also shown promise in some patients with COVID-19, with the RECOVERY[151] and REMAP-CAP[152] trials showing benefit in patients with hypoxia and in the intensive care unit[153–155]. These results led to the FDA approval of anti-IL-6R monoclonal antibodies as treatment for COVID-19. However, not all clinical studies using anti-IL-6R antibodies have shown clinical effectiveness, with some of the trials, such as COVACTA[156] and Kevzara[157], failing to improve clinical status or reduce patient mortality[158]. The EMPACTA[159] trial reduced the number of patients requiring mechanical ventilation by day 28 but did not improve survival[160]. Overall, the specific use of IL-6-blocking therapies to treat cytokine storm in COVID-19 has had mixed results. Beyond COVID-19, some, but not all, studies have also suggested beneficial effects of tocilizumab in cytokine storm associated with sJIA[26,161,162]. Emerging evidence suggests that anti-IL-6R antibodies may also have beneficial effects in patients with septic shock and cytokine storm[163,164], but the studies are retrospective or small, and larger randomized clinical trials are warranted to assess this effect.

Another cytokine targeted to reduce cytokine storm pathogenesis is IFNγ. The anti-IFNγ neutralizing antibody emapalumab is effective for primary HLH or cytokine storm that is refractory to conventional therapy[165]. Similarly, emapalumab has beneficial effects in patients with cytokine storm associated with Still disease that did not respond to high-dose glucocorticoids[166,167]. As IFNγ is an important component of antimicrobial host defence, these patients should be monitored for potential infectious complications, which should be promptly treated.

TNF-targeted therapies in cytokine storm should also be considered with care. Although some small case series have shown potential benefits in settings such as sepsis-associated hyperinflammation, MAS and severe COVID-19 (refs. 168–170), other studies show that anti-TNF therapy impairs host defence and increases susceptibility to secondary infections[171]. These mixed findings indicate that TNF blockade alone may not be universally effective and highlight the need for carefully designed combinatorial strategies. Such approaches should consider disease context, timing and patient-specific risk factors.

JAK inhibitors

Several of the pro-inflammatory cytokines associated with cytokine storm induce cellular activation cascades that involve JAK, for example, type II interferon (IFNγ) signals through JAK1 and JAK2, IL-2 through JAK1 and JAK3, IL-12 through JAK2, and IL-15 through JAK1 and JAK3. Additionally, TNF and IFNγ require JAK–STAT signalling to induce PANoptosis and drive the positive feedback loop between cell death and cytokine storm[2]. Given their critical role in cytokine signalling, JAK inhibitors have the potential to be broadly therapeutic in cytokine storm, and these inhibitors have been suggested as potential treatment[135]. In this respect, the JAK1–JAK2 inhibitor ruxolitinib improves outcomes in children with HLH[172]. Additionally, the JAK inhibitor baricitinib showed efficacy in COVID-19 (ref. 173).

Etoposide

Etoposide is a chemotherapeutic agent that causes DNA double-strand breaks by inhibiting topoisomerase II function. Etoposide has been used with good results in cytokine storm, especially in primary HLH[174]. In experimental models of hyperinflammation, etoposide selectively depletes activated T cells, providing a possible explanation for its effects in cytokine storm[175]. The combination of etoposide and steroids may also be beneficial in cases of severe or refractory secondary HLH caused by infection or cancer. However, the effect of etoposide on survival is less clear despite its beneficial biochemical response in cytokine storm[176]. In cytokine storm associated with rheumatic diseases, etoposide is typically reserved for second-line or third-line therapy[174].

Overall, treatments for cytokine storm are complex, and these generally target the different components of the pathophysiological process that lead to hyperinflammation. The heterogeneity of cytokine storm warrants individualized therapies in contrast to a single treatment across all cytokine storm cases. Additionally, successful treatment of cytokine storm should include aggressive therapy directed towards the underlying disease and immune signalling pathways and mechanisms causing the hyperinflammation to maximize benefit to the patient.

Quality of life

The long-term effect of cytokine storm on the quality of life of patients is currently an under-examined area in the literature. In patients who have cytokine storm secondary to a resolved trigger, the quality of life impacts may be less than in patients who have chronic cytokine storm. A study examining quality of life using the EuroQol 5-dimension 5-level questionnaire did not demonstrate any impact on quality of life at 3 months and 6 months following COVID-19 hyperinflammation syndrome[177]. By contrast, for paediatric patients diagnosed with HLH, quality of life (measured by the PedsQL 4.0 Parent Proxy Report) was lower than in healthy controls in the first year following diagnosis of HLH[178]. However, by 5 years post-diagnosis, quality of life was not statistically different between patients with a diagnosis of HLH and their peers without an HLH diagnosis[178]. This result implies that the impacts of cytokine storm on quality of life may not be permanent. Nevertheless, a better understanding of the impact of cytokine storm on quality of life is a key area for future research.

Outlook

Cytokine storm remains a complex and poorly understood spectrum of clinical manifestations that occurs as a result of multiple triggers. However, studies defining the underlying mechanisms that drive cytokine storm have demonstrated shared molecular events underlying cytokine storm, which provides great potential for improved therapeutic strategies in the future. Current research focused on developing new targeted therapies is leveraging our increasing understanding of how innate immune sensors and inflammatory cell death signalling pathways contribute to cytokine storm. As the molecular mechanisms regulating these processes continue to be defined, there will likely be

major advances in our ability to treat cytokine storm. Additionally, incorporating combinatorial therapies, such as blocking more than one cytokine simultaneously, can be considered to increase treatment success. In the preclinical setting, combined treatment with anti-TNF and anti-IFNγ antibodies improves survival in murine models of HLH, COVID-19 and sepsis, consistent with the synergy between TNF and IFNγ driving PANoptosis to perpetuate the positive feedback loop between inflammatory cell death and cytokine storm in these settings[2]. Furthermore, combination treatment with tocilizumab and anakinra, to block IL-6R and IL-1 together, may be beneficial in CAR T cell therapy-induced cytokine storm, as tocilizumab cannot cross the blood–brain barrier[149] but anakinra can prevent cytokine-related lethal neurotoxicity[179].

In addition, current evidence suggests that early and aggressive treatment provides the greatest benefit for patients with cytokine storm. However, identifying the therapeutic window for specific treatments is still an ongoing area of investigation. Clinical trials aimed at targeting cytokine storm have often fallen short of meeting their primary and/or secondary end points as the translation from preclinical to clinical studies is complicated by the need to optimize dosing strategies and overcome the narrow therapeutic windows in patients. Substantial effort is currently ongoing to improve animal models to more accurately reflect the inflammation experienced in patients. New models that can mimic the clinical symptoms of such a diverse spectrum of cytokine storm causes have been challenging to generate, and there are often differences in therapeutic outcomes between animal models and patients (animal models have been comprehensively reviewed elsewhere[180]). The combined administration of TNF and IFNγ in mice can recapitulate many of the clinical symptoms of cytokine storm[2] but additional models are needed to incorporate the upstream functions of cells that naturally produce these cytokines in patients. As these models are developed and optimized, the therapeutic development pipeline will be accelerated, and treatment strategies are likely to improve.

Another active area of work in the field is improving diagnostic and screening approaches. The current diagnostic workflow of cytokine storm and its underlying aetiology can often involve a complex series of tests, which is time-consuming and can lead to confusing diagnostic criteria. Given the rapid production of cytokines in these patients, even a brief delay in diagnosis can result in a substantial amplification of disease and a worsening of prognosis. Further work to identify specific biomarkers and a more specific list of clinical criteria for diagnosis is ongoing and urgently needed. Additionally, large-scale analyses of serum samples from patients to stratify risk groups based on cytokine levels are being considered to inform potential intervention strategies. As accessibility to high-level diagnostic techniques and personalized medicine grows, the potential to use diagnostic processes to select or design individualized host-directed immunotherapies for each patient will become available. Tailoring the approach to the patient's specific underlying disease aetiology will increase the chances of success. Interest is growing in using artificial intelligence-based and machine learning approaches to analyse large volumes of patient data to identify trends in clinical features and specific cytokine thresholds that will inform rapid diagnostics, which should translate to improved survival.

Overall, cytokine storm remains challenging in the current clinical setting; however, continued advances in understanding the basic biology as well as improved diagnostic approaches provide promise for the future of managing cytokine storm.

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